namely 2-(2-difluoromethoxy-benzylsulfonylmethyl)-*N*-[1-(5-ethyl[1,3,4]oxadiazole-2-carbonyl)butyl] 4-morpholin-4-yl-4-oxo butyramide. The Applicants traversed the Restriction Requirement.

In a non-final Office Action mailed June 11, 2003, the Examiner rejected Claim 30 under 35 U.S.C. § 101 as indefinite. In the same Office Action, Claim 10 was provisionally rejected under the doctrine of nonstatutory, obviousness-type double patenting, but the Examiner stated that this may be overcome by filing a terminal disclaimer and showing common ownership. Claims 8-9, 13-15 of the nonelected Group I and Claims 25-27 of the nonelected group III were objected to as non-elected subject matter and were withdrawn from further consideration by the Examiner. Claims 1-7, 11, 12, 16-24, 28, 29, and 31 were objected to as containing non-elected subject matter, but the Examiner stated they would be allowable if the non-elected invention within the claims is deleted.

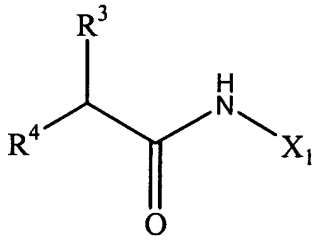
AMENDMENT

In the Claims:

Claims 1-29 and 31 have not been amended. The Applicants request that the Examiner cancel Claim 30.

AMENDMENTS TO THE CLAIMS

1. (original) A compound of Formula I:



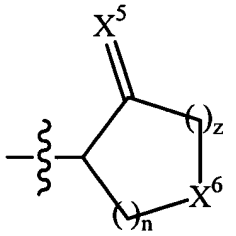
I

in which:

X^1 is $-C(R^1)(R^2)X^2$ or $-X^3$;

X^2 is cyano, -CHO, $-C(R^7)(R^8)R^5$, $-C(R^7)(R^8)CF_3$, $-C(R^7)(R^8)CF_2CF_2R^9$ $-CH=CHS(O)_2R^5$, $-C(R^7)(R^8)CF_2C(O)NR^5R^6$, $-C(R^7)(R^8)C(R^7)(R^8)NR^5R^6$, $-C(R^7)(R^8)C(R^7)(R^8)OR^5$, $-C(R^7)(R^8)CH_2OR^5$, $-C(R^7)(R^8)CH_2N(R^6)SO_2R^5$, $-C(R^7)(R^8)C(R^7)(R^8)N(R^6)(CH_2)_2OR^6$, $-C(R^7)(R^8)C(R^7)(R^8)N(R^6)(CH_2)_2NR^6$ or $-C(R^7)(R^8)C(R^7)(R^8)R^5$; wherein R^5 is (C_{1-4})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{4-10})aryl(C_{0-6})alkyl, (C_{4-10})cycloalkyl(C_{0-6})alkyl or hetero(C_{4-10})cycloalkyl(C_{0-6})alkyl; R^6 is hydrogen or (C_{1-6})alkyl; R^7 is hydrogen or (C_{1-4})alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo; R^9 is hydrogen, halo, (C_{1-4})alkyl, (C_{5-10})aryl(C_{0-6})alkyl or hetero(C_{5-10})aryl(C_{0-6})alkyl;

X^3 represents a group of Formula (a):



(a)

in which n is 1 or 2, z is 0 or 1, X^5 is selected from NR^{10}, S or O, wherein R^{10} is hydrogen or (C_{1-6})alkyl, and X^6 is O, S or NR^{11}, wherein R^{11} is selected from hydrogen, (C_{1-6})alkyl, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4S(O)_2R^{14}$, $-R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4C(O)NR^{12}R^{15}$ and $-X^4S(O)_2NR^{12}R^{15}$, in which X^4 is a bond or (C_{1-6})alkylene; R^{12} at each occurrence independently is hydrogen or (C_{1-6})alkyl; R^{13} is hydrogen, (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl, R^{14} is (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl and R^{15} is (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-12})bicycloaryl(C_{0-6})alkyl;

wherein within X^1 any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical R^{20} selected from $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{15}R^{12}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$; and wherein X^1 and R^{20} may be substituted further with 1 to 5 radicals independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$ wherein X^4, R^{12}, R^{13}, R^{14} and R^{15} are as defined above;

R^1 and R^2 are both fluoro; or

R^1 is hydrogen or (C_{1-6})alkyl and R^2 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, cyano, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{15}R^{12}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, wherein X^4, R^{12}, R^{13}, R^{14} and R^{15} are as defined above; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8})cycloalkylene or hetero(C_{3-8})cycloalkylene; wherein R^2, said cycloalkylene and said heterocycloalkylene may be substituted further with 1 to 3 radicals independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$,

$-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$, wherein X^4, R^{12}, R^{13} and R^{14} are as defined above;

R^3 and R^4 are independently $-C(R^{16})(R^{17})X^7$, wherein R^{16} and R^{17} are hydrogen, (C_{1-6})alkyl or fluoro, or R^{16} is hydrogen and R^{17} is hydroxy and X^7 is selected from $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{15}R^{12}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, wherein X^4, R^{12}, R^{13}, R^{14} and R^{15} are as defined above;

wherein within one of R^3 or R^4 any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical R^{21} selected from $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{12}R^{15}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, wherein X^4, R^{12} and R^{15} are as defined above; and wherein each of R^3, R^4 and R^{21} may be substituted further with 1 to 5 radicals independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$, wherein X^4, R^{12}, R^{13} and R^{14} are as defined above; provided that only one bicyclic ring structure is present within each of R^3 or R^4; and provided that when X^2 is cyano and X^7 within one of R^3 or R^4 is $-X^4C(O)R^{13}$ or $-X^4C(O)R^{15}$, wherein X^4 is a bond, then X^7 within the other of R^3 or R^4 is limited to $-X^4SR^{15}$, $-X^4S(O)R^{15}$ and $-X^4S(O)_2R^{15}$, wherein R^{15} is (C_{6-10})aryl(C_{1-6})alkyl substituted with 1 to 5 radicals or hetero(C_{5-10})aryl(C_{0-6})alkyl optionally substituted with 1 to 5 radicals, wherein said radicals are independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$,

$-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$, wherein X^4, R^{12}, R^{13} and R^{14} are as defined above, provided that the radical is not selected from only halo when R^{15} is (C_{6-10})aryl(C_{1-6})alkyl; and provided that when X^2 is cyano then X^7 within R^3 and R^4 is not $-X^4C(O)NR^{12}R^{12}$, $-X^4C(O)NR^{15}R^{12}$ or $-X^4C(O)NR^{18}R^{19}$, wherein X^4 is a bond and R^{18} and R^{19} together with the nitrogen atom to which they are attached form hetero(C_{3-10})cycloalkyl or hetero(C_{5-10})aryl;

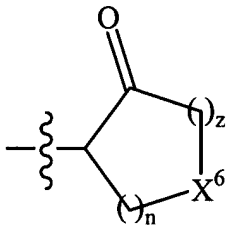
and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

2. (original) The compound of Claim 1 in which:

X^1 is $-C(R^1)(R^2)X^2$ or $-X^3$;

X^2 is cyano, -CHO, $-C(O)R^5$, $-C(O)CF_3$, $-C(O)CF_2CF_2R^9$ $-CH{=}CHS(O)_2R^5$, $-C(O)CF_2C(O)NR^5R^6$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$, $-C(O)C(O)N(R^6)(CH_2)_2OR^6$, $-C(O)C(O)N(R^6)(CH_2)_2NR^6$ or $-C(O)C(O)R^5$, wherein R^5 is (C_{1-4})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{4-10})aryl(C_{0-6})alkyl, (C_{4-10})cycloalkyl(C_{0-6})alkyl or hetero(C_{4-10})cycloalkyl(C_{0-6})alkyl, R^6 is hydrogen or (C_{1-6})alkyl and R^9 is halo;

X^3 represents a group of Formula (b):



(b)

in which n is 1 or 2, z is 0 or 1, X^6 is O or NR^{11}, wherein R^{11} is selected from hydrogen, (C_{1-6})alkyl, $-X^4OC(O)R^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4S(O)_2R^{14}$, $-R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4C(O)NR^{12}R^{15}$ and $-X^4S(O)_2NR^{12}R^{15}$, in which X^4 is a bond or (C_{1-6})alkylene; R^{12} at each occurrence independently is hydrogen or (C_{1-6})alkyl; R^{13} is

hydrogen, (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl, R^{14} is (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl and R^{15} is (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-12})bicycloaryl(C_{0-6})alkyl;

wherein within X^1 any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical selected from $-R^{15}$ and $-X^4C(O)R^{15}$; and wherein X^1 may be substituted further with 1 to 3 radicals independently selected from (C_{1-6})alkyl, halo-substituted(C_{1-4})alkyl, $-X^4NR^{12}R^{12}$, $-X^4OR^{13}$ and $-X^4S(O)_2R^{14}$, wherein X^4, R^{12}, R^{13}, R^{14} and R^{15} are as defined above;

R^1 and R^2 are both fluoro; or

R^1 is hydrogen or (C_{1-6})alkyl and R^2 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, $-X^4OR^{13}$ and $-R^{15}$; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8})cycloalkylene or hetero(C_{3-8})cycloalkylene; wherein R^2 may be substituted further with (C_{1-6})alkyl; wherein X^4, R^{13} and R^{15} are as defined above;

R^3 and R^4 are independently $-C(R^{16})(R^{17})X^7$, wherein R^{16} and R^{17} are hydrogen, (C_{1-6})alkyl or fluoro, or R^{16} is hydrogen and R^{17} is hydroxy and X^7 is selected from $-X^4SR^{13}$, $-X^4C(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$ and $-X^4C(O)NR^{15}R^{12}$, wherein X^4, R^{12}, R^{13} and R^{15} are as defined above;

wherein within one of R^3 or R^4 any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical selected from $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{12}R^{15}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, wherein X^4, R^{12} and R^{15} are as defined above; and wherein each of R^3 and R^4 may be substituted further with 1 to 5 radicals independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$, wherein X^4, R^{12}, R^{13} and R^{14} are as defined above;

wherein within one of R^3 and R^4 any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical selected from $-R^{15}$ and $-X^4OR^{15}$; and wherein each of R^3 or R^4 may be substituted further by 1-5 radicals independently selected from (C_{1-6})alkyl, cyano, halo,

halo-substituted(C_{1-4})alkyl, $-X^4NR^{12}C(O)OR^{12}$, $-X^4OR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$ and $-X^4S(O)_2R^{14}$, wherein X^4, R^{12}, R^{13}, R^{14} and R^{15} are as defined above;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

3. (original) A compound of claim 2 in which R^3 and R^4 are independently $-CH_2X^7$, wherein X^7 is selected from X^4SR^{13}, $-X^4C(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$ and $-X^4C(O)NR^{15}R^{12}$, wherein X^4 is a bond or (C_{1-6})alkylene, R^{12} at each occurrence independently is hydrogen or (C_{1-6})alkyl, R^{13} is hydrogen, (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl, R^{14} is (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl and R^{15} is (C_{3-10})cycloalkyl(C_{0-6})alkyl, (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-12})bicycloaryl(C_{0-6})alkyl; wherein within R^3 and R^4 any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical selected from $-R^{15}$ and $-X^4OR^{15}$, wherein X^4 and R^{15} are as defined above; and wherein R^3 and R^4 may be substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, $-X^4NR^{12}C(O)OR^{12}$, $-X^4OR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$ and $-X^4S(O)_2R^{14}$, wherein X^4 R^{12}, R^{13} and R^{14} are as defined above;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

4. (original) A compound of claim 3 in which R^3 is selected from 5-bromo-thiophen-2-ylmethyl, 3-cyclohexylpropyl, 2-cyclohexylpropyl, 2-cyclopentylpropyl, 3-phenylpropyl, 3-(2-difluoromethoxy)phenylpropyl, 2-phenylcyclopropylmethyl, 2,2-difluoro-3-phenylpropyl, 1-benzylcyclopropylmethy, 2-tetrahydro-pyran-4-ylethyl, 1-isobutylcyclopropylmethyl, thiophen-2-

ylmethyl, tetrahydro-pyran-4-ylmethyl, cyclopropylmethylsulfanylmethyl, 2,2-dimethyl-3-phenylpropyl, 4-methyl-[1,2,5]thiadiazol-3-ylmethylsulfonylmethyl, 3-methyl-[1,2,4]thiadiazol-3-ylmethylsulfonylmethyl, thiophen-3-ylmethylsulfonylmethyl, 3-methoxy-5-methyl-isoxazol-4-ylmethylsulfonylmethyl, 2,4-dimethyl-thiazol-5-ylmethylsulfonylmethyl, 2-methyl-oxazol-4-ylmethylsulfonylmethyl, 2-methyl-thiazol-4-ylmethylsulfonylmethyl,, 1,2,3]thiadiazol-4-ylmethylsulfonylmethyl, 3-methyl-[1,2,4]thiadiazol-5-ylmethylsulfonylmethyl, 4-methyl-[1,2,5]thiadiazol-3-ylmethylsulfonylmethyl, thiophen-3-ylmethylsulfonylmethyl, tetrahydro-pyran-4-yloxymethyl, piperidin-1-ylcarbonyl, thiophene-2-sulfonylmethyl, 3-chloro-2-fluoro-benzylsulfonylmethyl, benzenesulfonylmethyl, benzylsulfonylmethyl, 2-(1,1-difluoro-methoxy)-benzylsulfonylmethyl, 2-benzenesulfonyl-ethyl, 2-(pyridine-2-sulfonyl)-ethyl, 2-(pyridine-4-sulfonyl)-ethyl, 2-benzylsulfonyl-ethyl, oxy-pyridin-2-ylmethylsulfonylmethyl, prop-2-ene-1-sulfonylmethyl, 4-methoxy-benzylsulfonylmethyl, *p*-tolylmethylsulfonylmethyl, 4-chloro-benzylsulfonylmethyl, *o*-tolylmethylsulfonylmethyl, 3,5-dimethyl-benzylsulfonylmethyl, 4-trifluoromethyl-benzylsulfonylmethyl, 4-trifluoromethoxy-benzylsulfonylmethyl, 2-bromo-benzylsulfonylmethyl, pyridin-2-ylmethylsulfonylmethyl, pyridin-3-ylmethylsulfonylmethyl, pyridin-4-ylmethylsulfonylmethyl, naphthalen-2-ylmethylsulfonylmethyl, 3-methyl-benzylsulfonylmethyl, 3-trifluoromethyl-benzylsulfonylmethyl, 3-trifluoromethoxy-benzylsulfonylmethyl, 4-fluoro-2-trifluoromethoxy-benzylsulfonylmethyl, 2-fluoro-6-trifluoromethyl-benzylsulfonylmethyl, 3-chloro-benzylsulfonylmethyl, 2-fluoro-benzylsulfonylmethyl, 2-trifluoro-benzylsulfonylmethyl, 2-cyano-benzylsulfonylmethyl, 4-*tert*-butyl-benzylsulfonylmethyl, 2-fluoro-3-methyl-benzylsulfonylmethyl, 3-fluoro-benzylsulfonylmethyl, 4-fluoro-benzylsulfonylmethyl, 2-chloro-benzylsulfonylmethyl, 2,5-difluoro-benzylsulfonylmethyl, 2,6-difluoro-benzylsulfonylmethyl, 2,5-dichloro-benzylsulfonylmethyl, 3,4-dichloro-benzylsulfonylmethyl, 2-(1,1-difluoro-methoxy)-benzylsulfonylmethyl, 2-cyano-benzylsulfonylmethyl, 3-cyano-benzylsulfonylmethyl, 2-trifluoromethoxy-benzylsulfonylmethyl, 2,3-difluoro-benzylsulfonylmethyl, 2,5-difluoro-benzylsulfonylmethyl, biphenyl-2-ylmethylsulfonylmethyl, cyclohexylmethyl, 3-fluoro-benzylsulfonylmethyl, 3,4-difluoro-benzylsulfonylmethyl, 2,4-difluoro-benzylsulfonylmethyl,

2,4,6-trifluoro-benzylsulfonylmethyl, 2,4,5-trifluoro-benzylsulfonylmethyl, 2,3,4-trifluoro-benzylsulfonylmethyl, 2,3,5-trifluoro-benzylsulfonylmethyl, 2,5,6-trifluoro-benzylsulfonylmethyl, 2-chloro-5-trifluoromethylbenzylsulfonylmethyl, 2-methyl-propane-1-sulfonyl, 2-fluoro-3-trifluoromethylbenzylsulfonylmethyl, 2-fluoro-4-trifluoromethylbenzylsulfonylmethyl, 2-fluoro-5-trifluoromethylbenzylsulfonylmethyl, 4-fluoro-3-trifluoromethylbenzylsulfonylmethyl, 2-methoxy-benzylsulfonylmethyl, 3,5 bis-trifluoromethyl-benzylsulfonylmethyl, 4-difluoromethoxy-benzylsulfonylmethyl, 2-difluoromethoxy-benzylsulfonylmethyl, 3-difluoromethoxy-benzylsulfonylmethyl, 2,6-dichloro-benzylsulfonylmethyl, biphenyl-4-ylmethylsulfonylmethyl, 3,5-dimethyl-isoxazol-4-ylmethylsulfonylmethyl, 5-chloro-thiophen-2-ylmethylsulfonylmethyl, 2-[4-(1,1-Difluoro-methoxy)-benzenesulfonyl]-ethyl, 2-[2-(1,1-Difluoro-methoxy)-benzenesulfonyl]-ethyl, 2-[3-(1,1-Difluoro-methoxy)-benzenesulfonyl]-ethyl, 2-(4-trifluoromethoxy-benzenesulfonyl)-ethyl, 2-(3-trifluoromethoxy-benzenesulfonyl)-ethyl, 2-(2-trifluoromethoxy-benzenesulfonyl)-ethyl, (cyanomethyl-methyl-carbamoyl)-methyl, biphenyl-3-ylmethyl, 2-oxo-2-pyrrolidin-1-yl-ethyl, 2-benzenesulfonyl-ethyl, isobutylsulfanylmethyl, 2-phenylsulfanyl-ethyl, cyclohexylmethylsulfonylmethyl, 2-cyclohexyl-ethanesulfonyl, benzyl, naphthalen-2-yl, benzylsulfanylmethyl, 2-trifluoromethyl-benzylsulfanylmethyl, phenylsulfanyl-ethyl and cyclopropylmethylsulfonylmethyl;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

5. (original) A compound of claim 4 in which R^4 is selected from 2-trifluorobenzylsulfonylmethyl, 3-phenylsulfanylpropyl, 4-chlorobenzylsulfonylmethyl, thiophen-2-ylsulfonylmethyl, benzylsulfonylmethyl, 4-methylbenzylsulfonylmethyl, 2-phenylsulfonylethyl, 2-pyridin-2-ylsulfonylethyl, 2-pyridin-4-ylsulfonylethyl, 2-benzylsulfonylethyl, 2-(3-difluoromethoxyphenylsulfonyl)ethyl, naphthalen-2-ylmethylsulfonylmethyl, pyridin-2-ylmethylsulfonylmethyl, 3-methylbenzylsulfonylmethyl,

3-trifluoromethylbenzylsulfonylmethyl, 3-difluoromethoxybenzylsulfonylmethyl, 3-chlorobenzylsulfonylmethyl, 3-fluorobenzylsulfonylmethyl, 4-fluorobenzylsulfonylmethyl, 3-cyanobenzylsulfonylmethyl, 4-cyanobenzylsulfonylmethyl, 3,4-difluorobenzylsulfonylmethyl, benzylsulfonylmethyl, *N*-cyanomethyl-*N*-methylcarbamoylmethyl, 3-bromobenzyl, 4-phenylbutyl, 2,2-difluoro-3-phenylpropyl, 4'-methylsulfonylaminobiphenyl-3-ylmethyl, 4'-ethoxycarbonylaminobiphenyl-3-ylmethyl, 4-methylpiperazin-1-ylcarbonylmethyl, 1-fluoro-2-(4-methylpiperazin-1-yl)-2-oxoethyl, 1-hydroxy-4-methylpiperazin-1-yl-2-oxoethyl, 1-hydroxy-2-morpholin-4-yl-2-oxoethyl, 1-hydroxy-2-oxo-2-pyrrolidin-1-yl-ethyl, 1-fluoro-2-oxo-2-pyrrolidin-1-yl-ethyl, 1-fluoro-2-isopropylamino-2-oxoethyl, 1-hydroxy-2-isopropylamino-2-oxoethyl, 1-fluoro-2-oxo-2-piperazin-1-ylethyl, thiophen-3-ylmethylsulfonylmethyl, 4-methyl-[1,2,5]thiadiazol-3-ylmethylsulfonylmethyl, 3-methoxy-5-methyl-isoxazol-4-ylmethylsulfonylmethyl, 2,4-dimethyl-thiazol-5-ylmethylsulfonylmethyl, 2-methyl-oxazol-4-ylmethylsulfonylmethyl, 2-methyl-thiazol-4-ylmethylsulfonylmethyl, 2-([1,2,3]thiadiazol-4-ylmethylsulfonyl)-ethyl, 2-(3-methyl-[1,2,4]thiadiazol-5-ylmethylsulfonyl)-ethyl, 2-oxo-2-phenyl-ethyl, 2-morpholin-4-yl-2-oxo-ethyl, 2-benzenesulfonyl-ethyl, 2-naphthalen-2-yl-2-oxo-ethyl, 2-benzo[1,3]dioxol-5-yl-2-oxo-ethyl, 2-benzo[*b*]thiophen-2-yl-2-oxo-ethyl, 2-biphenyl-4-yl-2-oxo-ethyl, 4-benzylsulfonylmethyl, 2-(3-trifluoromethoxy-benzenesulfonyl)-ethyl, 2-oxo-2-(4-phenoxy-phenyl)-ethyl, 2-(4-hydroxy-phenyl)-2-oxo-ethyl, benzylcarbamoyl-methyl, 4-acetyl-piperazine-1-carboxylic acid ethyl ester, cyclohexylcarbamoylmethyl, 2-(3-Chloro-benzo[*b*]thiophen-2-yl)-2-oxo-ethyl, benzenesulfonylmethyl, 2-oxo-2-thiophen-2-yl-ethyl, 2-oxo-2-thiophen-3-yl-ethyl, naphthalene-2-sulfonylmethyl, 2-(5-methyl-thiophen-2-yl)-2-oxo-ethyl, 2-(3-chloro-thiophen-2-yl)-2-oxo-ethyl, 5-methyl-thiophene-2-sulfonylmethyl, phenylcarbamoylmethyl, (5,6,7,8-tetrahydro-naphthalen-1-ylcarbamoyl)-methyl, (4-carbamoyl-phenylcarbamoyl)-methyl, (3-carbamoyl-phenylcarbamoyl)-methyl, (butyl-methyl-carbamoyl)-methyl, biphenyl-4-ylmethyl, 2-oxo-2-*p*-tolyl-ethyl, 2-(3-fluoro-4-methoxy-phenyl)-2-oxo-ethyl, 2-(4-chloro-phenyl)-2-oxo-ethyl, 2-(4-methoxy-phenyl)-2-oxo-ethyl, 2-oxo-2-(4-trifluoromethoxy-phenyl)-ethyl, 2-(3,4-difluoro-phenyl)-2-oxo-ethyl, 2-(3,4-dimethoxy-phenyl)-2-oxo-ethyl, 2-(4-fluoro-phenyl)-2-oxo-ethyl, 5-methyl-2-oxo-hexyl, 3,5-dimethyl-benzylsulfonylmethyl, 4-trifluoromethyl-benzylsulfonylmethyl; 4-trifluoromethoxy-benzylsulfonylmethyl,

isopropylcarbamoyl-methyl, 4-dimethylcarbamoylmethyl, pyridin-4-ylcarbamoylmethyl, pyridin-4-ylmethylsulfonylmethyl, pyridin-3-ylmethylsulfonylmethyl, 3,4-dichloro-benzylsulfonylmethyl, pyridin-3-ylcarbamoylmethyl, 4-methoxy-benzylsulfonylmethyl, 4-chloro-benzylsulfonylmethyl, thiophene-2-sulfonylmethyl, benzylsulfonylmethyl, *p*-tolylmethylsulfonylmethyl, 2-benzenesulfonyl-ethyl, 2-(pyridine-2-sulfonyl)-ethyl, 2-(pyridine-4-sulfonyl)-ethyl, 2-benzylsulfonyl-ethyl, 2-[3-(1,1-Difluoro-methoxy)-benzenesulfonyl]-ethyl, naphthalen-2-ylmethylsulfonylmethyl, pyridin-2-ylmethylsulfonylmethyl, *m*-tolylmethylsulfonylmethyl, 3-trifluoromethyl-benzylsulfonylmethyl, 3-trifluoromethoxy-benzylsulfonylmethyl, 3-chloro-benzylsulfonylmethyl, 3-fluoro-benzylsulfonylmethyl, 4-fluoro-benzylsulfonylmethyl, 3-cyano-benzylsulfonylmethyl, 4-cyano-benzylsulfonylmethyl, 3,4-difluoro-benzylsulfonylmethyl, (cyanomethyl-methyl-carbamoyl)-methyl, 3-bromo-benzyl, 2-oxo-2-pyrrolidin-1-yl-ethyl, 2-(4'-chloro-biphenyl-4-yl)-2-oxo-ethyl, biphenyl-3-ylmethyl, 2-(1,1-difluoro-methoxy)-benzylsulfonylmethyl, 2-(4-methylsulfonylamino-phenyl)-2-oxo-ethyl, 2-oxo-2-piperidin-1-yl-ethyl, 2-(4-methylsulfonyl-piperazin-1-yl)-2-oxo-ethyl, 2-trifluoromethyl-benzylsulfonylmethyl, 4-fluoro-3-trifluoromethyl-benzylsulfonylmethyl, 4-carboxy-benzylsulfonylmethyl, 3,5-bis-trifluoromethyl-benzylsulfonylmethyl, 4-(1,1-difluoro-methoxy)-benzylsulfonylmethyl, 3-(1,1-difluoro-methoxy)-benzylsulfonylmethyl, 5-chloro-thiophen-2-ylmethylsulfonylmethyl, 2-[4-(1,1-difluoro-methoxy)-benzenesulfonyl]-ethyl, 2-(4-trifluoromethoxy-benzenesulfonyl)-ethyl, 2-phenylsulfanyl-ethyl, benzylsulfanylmethyl, 2-trifluoromethyl-benzylsulfanylmethyl, 2-trifluoromethoxy-benzylsulfanylmethyl, 2-cyclohexyl-ethyl and isobutylsulfanylmethyl;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

6. (original) The compound of claim 5 in which R^1 is hydrogen or (C_{1-6})alkyl and R^2 is hydrogen, $-X^4OR^{13}$, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{5-10})aryl(C_{0-6})alkyl or (C_{1-6})alkyl; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8})cycloalkylene or

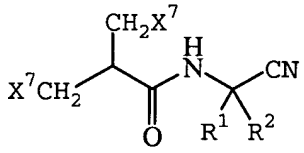
hetero(C_{3-8})cycloalkylene; wherein the cycloalkylene or heterocycloalkylene are optionally substituted with 1 to 3 (C_{1-6})alkyl radicals;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

7. (original) The compound of claim 6 in which R^1 is hydrogen or methyl and R^2 is methoxymethyl, methoxyethyl, methyl, ethyl, propyl, butyl, phenethyl, hiophen-2-yl or 5-methyl-furan-2-yl; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form cyclopropyl, tetrahydro-pyran-4-yl or 1-methyl-piperidin-4-yl;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

8. (original) The compound of claim 7 of Formula I(a):



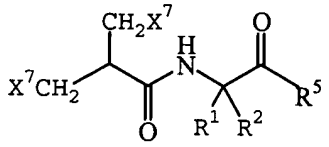
I(a)

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

9. (original) The compound of claim 8 selected from the group consisting of 3-biphenyl-3-yl-*N*-cyanomethyl-2-benzylsulfonylmethyl-propionamide; 3-biphenyl-4-yl-*N*-cyanomethyl-2-benzylsulfonylmethyl-propionamide; 3-(3-bromo-phenyl)-*N*-cyanomethyl-2-benzylsulfonylmethyl-propionamide; *N*-cyanomethyl-3-(3-cyano-benzylsulfonyl)-2-benzylsulfonyl-methyl-propionamide; *N*-cyanomethyl-2-[2-1,1-difluoro-methoxy)-benzylsulfanylmethyl]-3-benzylsulfanyl-propionamide; *N*-cyanomethyl-3-(2-trifluoromethyl-benzylsulfanyl)-2-(2-trifluoro-methyl-benzylsulfanylmethyl)-propionamide; *N*-cyanomethyl-3-isobutylsulfanyl-2-isobutylsulfanylmethyl-propionamide; *N*-cyanomethyl-4-phenylsulfanyl-2-(2-phenylsulfanyl-ethyl)-butyramide; *N*-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-benzylsulfanyl]-2-[2-(1,1-difluoro-methoxy)-benzylsulfanylmethyl]-propionamide; 3-benzylsulfanyl-2-benzylsulfanylmethyl-*N*-cyanomethyl-propionamide; *N*-cyanomethyl-2-[2-1,1-difluoro-methoxy)-benzylsulfonylmethyl]-3-benzylsulfonyl-propionamide; *N*-cyanomethyl-3-(2-trifluoromethyl-benzylsulfonyl)-2-(2-trifluoromethyl-benzylsulfonylmethyl)-propionamide; 4-benzenesulfonyl-2-(2-benzenesulfonyl-ethyl)-*N*-cyanomethyl-butyramide; *N*-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-benzylsulfonyl]-2-[2-(1,1-difluoro-methoxy)-benzylsulfonylmethyl]-propionamide; *N*-cyanomethyl-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide; *N*-cyanomethyl-3-(2-methyl-propane-1-sulfonyl)-2-(2-methyl-propane-1-sulfonylmethyl)-propionamide; *N*-cyanomethyl-3-(2-methyl-thiazol-4-ylmethylsulfonyl)-2-benzyl-sulfonylmethyl-propionamide; 3-biphenyl-3-yl-*N*-cyanomethyl-2-[2-(1,1-difluoro-methoxy)-benzyl-sulfonylmethyl]-propionamide; (3'-{2-(cyanomethyl-carbamoyl)-3-[2-(1,1-difluoro-methoxy)-benzyl-sulfonyl]-propyl}-biphenyl-4-yl)-carbamic acid ethyl ester; *N*-cyanomethyl-2-[2-(1,1-difluoro-methoxy)-benzylsulfonylmethyl]-3-(4'-methylsulfonylamino-biphenyl-3-yl)-propionamide; 3-(3-bromo-phenyl)-*N*-cyanomethyl-2-[2-(1,1-difluoro-methoxy)-phenyl-methylsulfonylmethyl]-propionamide; *N*-cyanomethyl-2-((E)-3-phenyl-allyl)-3-benzylsulfonyl-propionamide; and *N*-cyanomethyl-3-benzylsulfonyl-2-(3-phenyl-propyl)-propionamide;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

10. (original) The compound of Claim 7 of Formula I(b):



I(b)

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

11. (original) The compound of claim 10 in which R^5 is 1*H*-benzoimidazol-2-yl, benzooxazol-2-yl, oxazolo[4,5-b]pyridin-2-yl, benzothiazol-2-yl, 5-phenyl-[1,3,4]oxadiazol-2-yl, 4-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-yl, 5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl, 5-pyridazin-3-yl-[1,3,4]oxadiazol-2-yl, pyrimidin-2-yl, pyridazin-3-yl, 3-penyl-[1,2,4]oxadiazol-5-yl, 5-methoxymethyl-[1,3,4]oxadiazol-2-yl, 5-ethyl-[1,3,4]oxadiazol-2-yl,, 1,3,4]thiadiazol-2-yl, benzyloxycarbonyl, benzyloxydicarbonyl, phenyldicarbonyl, 5-methyl-[1,3,4]thiadiazol-2-yl, 5-trifluoromethyl-[1,3,4]oxadiazol-2-yl, 5-methyl-[1,3,4]oxadiazol-2-yl, 5-methyl-[1,2,4]oxadiazol-3-yl, 5-phenyl-[1,2,4]oxadiazol-3-yl, 5-thiophen-3-yl-[1,2,4]oxadiazol-3-yl, 5-trifluoromethyl-[1,2,4]oxadiazol-3-yl, 3-methyl-[1,2,4]oxadiazol-5-yl or 3-pyrazin-2-yl;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

12. (original) The compound of claim 11 selected from the group consisting of *N*-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide; *N*-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-3-(2-trifluoromethyl-benzylsulfonyl)-2-(2-trifluoromethyl-benzylsulfonylmethyl)-propionamide; *N*-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-pentyl]-4-(2-methoxy-benzenesulfonyl)-2-[2-(2-methoxy-benzenesulfonyl)-ethyl]-butyramide; 4-Benzenesulfonyl-

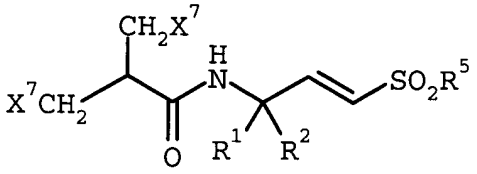
2-(2-benzenesulfonyl-ethyl)-*N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-butyramide; (R)-*N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-cyclohexylmethyl-3-benzylsulfonyl-propionamide; *N*-[(S)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide; *N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-3-cyclohexyl-2-cyclohexylmethyl-propionamide; *N*-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-3-isobutylsulfanyl-2-isobutylsulfanylmethyl-propionamide; *N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-3-benzylsulfanyl-2-benzylsulfanylmethyl-propionamide; *N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-4-phenylsulfanyl-2-(2-phenylsulfanyl-ethyl)-butyramide; *N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide; *N*-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-pentyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide; 4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-{(S)-1-[1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-methanoyl]-propyl}-butyramide; *N*-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-2-[2-(1,1-difluoro-methoxy)-benzylsulfonylmethyl]-3-benzylsulfonyl-propionamide; 4-Morpholin-4-yl-4-oxo-*N*-[1-(2-oxo-2-phenyl-acetyl)-pentyl]-2-benzylsulfonylmethyl-butyramide; *N*-(1,1-Dimethyl-2-oxazolo[4,5-b]pyridin-2-yl-2-oxo-ethyl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide; *N*-[1-(5-Ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide; *N*-[1-(5-Ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-oxo-2-benzylsulfonyl-methyl-4-piperidin-1-yl-butyramide; *N*-[1-(5-Ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-oxo-2-benzylsulfonyl-methyl-4-pyrrolidin-1-yl-butyramide; *N*-[1-(5-Methoxymethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide; *N*-[1-(5-Methoxymethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide; *N*-[1-(5-Methoxymethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide; 4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; 4-Oxo-2-benzylsulfonylmethyl-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-piperidin-1-yl-butyramide; 4-Oxo-2-benzylsulfonylmethyl-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-pyrrolidin-1-yl-butyramide; 4-Morpholin-4-yl-*N*-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-butyramide; *N*-[1-(Oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonyl-methyl-4-piperidin-1-yl-butyramide; *N*-[1-(Oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonyl-methyl-4-pyrrolidin-1-yl-butyramide; 4-Morpholin-4-yl-4-oxo-2-

benzylsulfonylmethyl-*N*-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; 4-Oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-*N*-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; 4-Oxo-2-benzylsulfonylmethyl-*N*-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-pyrrolidin-1-yl-butyramide; 4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-[1-(5-pyridin-3-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; *N*-[1-(Benzooxazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide; *N*-[1-(Benzooxazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide; *N*-[1-(Benzooxazole-2-carbonyl)-propyl]-2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyramide; 2-Cyclohexylmethyl-4-morpholin-4-yl-*N*-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-butyramide; 2-Cyclohexylmethyl-N-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-morpholin-4-yl-4-oxo-butyramide; *N*-(2-Benzooxazol-2-yl-1-methoxymethyl-2-oxo-ethyl)-2-(2-difluoromethoxy-benzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide; *N*-[1-(Benzooxazole-2-carbonyl)-propyl]-2-(2-cyclohexyl-ethyl)-4-morpholin-4-yl-4-oxo-butyramide; 2-(2-Cyclohexyl-ethyl)-4-morpholin-4-yl-*N*-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-butyramide; 2-(2-Cyclohexyl-ethyl)-4-morpholin-4-yl-4-oxo-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; 2-(2-Difluoromethoxy-benzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; 2-(2-Difluoromethoxy-benzylsulfonylmethyl)-*N*-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-morpholin-4-yl-4-oxo-butyramide; *N*-[1-(Benzooxazole-2-carbonyl)-propyl]-2-(2-difluoromethoxy-benzyl-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide; 2-(2-Morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, 1-(benzooxazole-2-carbonyl)-propyl]-amide; (R)-2-Cyclohexylmethyl-4-morpholin-4-yl-4-oxo-*N*-[(S)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propyl]-butyramide; 2-(2-Morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, (S)-1-(5-phenyl-[1,2,4]oxadiazole-3-carbonyl)-propyl]-amide; 4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-[(S)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propyl]-butyramide; (R)-2-Cyclohexylmethyl-4-morpholin-4-yl-4-oxo-*N*-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-butyramide; 4-Morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-4-oxo-2-benzylsulfonylmethyl-butyramide; *N*-(1,1-Dimethyl-2-oxazol-2-yl-2-oxo-ethyl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide; *N*-4-Isopropyl-*N*-1-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-2-benzylsulfonylmethyl-succinamide; 2-(2-Difluoromethoxy-benzylsulfonylmethyl)-4-morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-4-oxo-butyramide; 2-(2-Methyl-propane-

1-sulfonylmethyl)-4-morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-4-oxo-butyramide; 2-Cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-4-oxo-butyramide; *N*-[1-(Benzooxazole-2-carbonyl)-butyl]-2-benzylsulfonyl-3-(tetrahydro-pyran-4-yloxymethyl)-propionamide; *N*-[1-(Benzooxazole-2-carbonyl)-butyl]-3-ethanesulfonyl-2-(tetrahydro-pyran-4-yloxymethyl)-propionamide; *N*-(1-Benzenesulfonyl-3-oxo-azepan-4-yl)-2-cyclopropylmethylsulfonyl-methyl-4-morpholin-4-yl-4-oxo-butyramide; 2-Cyclopropylmethylsulfonylmethyl-N-{(S)-1-[(R)-hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl}-4-morpholin-4-yl-4-oxo-butyramide; *N*-{(S)-1-[(R)-hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl}-2-(2-methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide; 2-(2-Morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid {(S)-1-[(R)-hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl}-amide; 2-Cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-N-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-butyramide; 2-(2-methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-N-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-butyramide; 2-(2-Morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, (S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl}-amide; *N*-[(1S)-1-(Benzooxazol-2-yl-hydroxy-methyl)-3-phenyl-propyl]-2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyramide; (R)-2-((S)-1-Hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, 1-(benzoxazole-2-carbonyl)-propyl]-amide; (R)-5-(2-Difluoromethoxy-phenyl)-2-((S)-1-hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-pentanoic acid, 1-(benzoxazole-2-carbonyl)-propyl]-amide; and 4-Morpholin-4-yl-N-[1-(oxazole-2-carbonyl)-cyclopropyl]-4-oxo-2-benzylsulfonyl methyl –butyramide;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

13. (original) The compound of claim 7 of Formula I(c):



I(c)

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

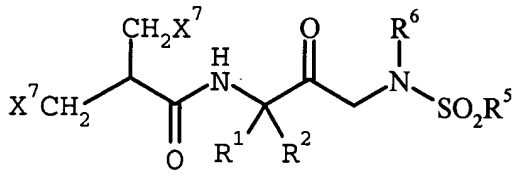
14. (original) The compound of claim 13 in which R^5 is phenyl;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

15. (original) The compound of claim 14 selected from the group consisting of *N*-[(S)-1-((E)-2-benzenesulfonyl-vinyl)-pentyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide and *N*-(3-benzenesulfonyl-1-phenethyl-allyl)-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

16. (original) The compound of claim 7 of Formula I(d):



I(d)

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

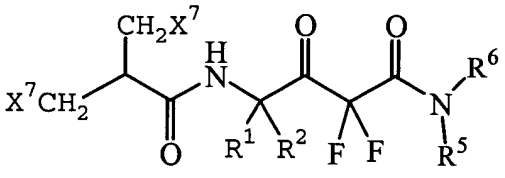
17. (original) The compound of claim 16 in which R^5 is phenyl and R^6 is hydrogen;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

18. (original) The compound of claim 17 namely *N*-(3-benzenesulfonylamino-2-oxo-propyl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

19. (original) The compound of claim 7 of Formula I(e):



I(e)

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

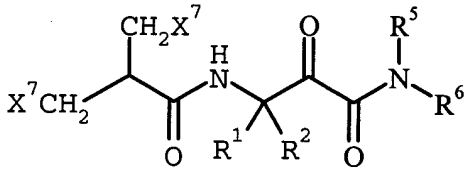
20. (original) The compound of claim 19 in which R^5 and R^6 is methyl;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

21. (original) The compound of claim 20 in which one X^7 is morpholine-4-carbonyl and the other is benzylsulfonyl, R^1 is hydrogen and R^2 is ethyl, namely (S)-2,2-difluoro-4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butanoylamino)-3-oxo-hexanoic acid dimethylamide;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

22. (original) The compound of claim 7 of Formula I(f):



I(f)

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such

compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

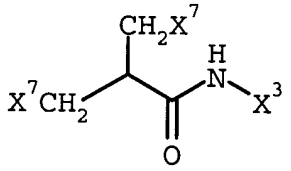
23. (original) The compound of claim 22 in which R^5 is methyl, benzyl, phenethyl, cyclohexyl, methoxyethyl, dimethylaminoethyl, tetrahydro-pyran-4-yl, 1-methylsulfonyl-piperidin-4-yl, 4-methyl-piperazin-1-yl, morpholin-4-ylethyl, pyridin-2-yl, pyridin-2-ylmethyl or oxazol-2-ylmethyl; R^6 is hydrogen or methyl; or R^5 and R^6 together with the nitrogen atom to which both R^5 and R^6 are attached form morpholine-4-yl, pyrrolidin-1-yl, 4-dimethylamino-piperazin-1-yl, 4-hydroxy-piperazin-1-yl, 4-pyridin-2-yl-piperazin-1-yl, 4-benzoyl-piperazin-1-yl or 3-oxo-piperazin-1-yl;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

24. (original) The compound of claim 23 selected from the group consisting of *N*-[(S)-1-(1-Benzylcarbamoyl-methanoyl)-propyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide and *N*-[(S)-1-(1-Benzylcarbamoyl-methanoyl)-propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

25. (original) The compound of claim 7 of Formula I(g):



I(g)

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

26. (original) The compound of claim 25 in which X^3 is 1-benzoyl-4-oxo-pyrrolidin-3-yl, 4-oxo-pyrrolidin-3-yl-1-carboxylic acid tert-butyl ester, 2-methyl-4-oxo-tetrahydro-furan-3-yl, 2-ethyl-4-oxo-tetrahydro-furan-3-yl, 4-oxo-tetrahydro-furan-3-yl, 2-acetoxy-4-oxo-azetidin-3-yl, 1-isopropyl-3-oxo-azepan-4-yl, 3-oxo-azepan-4-yl-1-carboxylic acid benzyl ester, 3-oxo-azepan-4-yl-1-carboxylic acid tert-butyl ester, 1-benzoyl-3-oxo-azepan-4-yl, 1-isobutyryl-3-oxo-azepan-4-yl, 3-oxo-1-(propane-2-sulfonyl)-azepan-4-yl, 1-benzenesulfonyl-3-oxo-azepan-4-yl, 1-benzenesulfonyl-3-oxo-piperidin-4-yl, 1-benzenesulfonyl-4-oxo-pyrrolidin-3-yl, 1-benzoyl-3-oxo-piperidin-4-yl or 3-oxo-tetrahydro-pyran-4-yl;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

27. (original) The compound of claim 23 selected from the group consisting of 3-Hydroxy-4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-azepane-1-carboxylic acid tert-butyl ester; 4-(2-Cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyrylamino)-3-hydroxy-azepane-1-carboxylic acid tert-butyl ester; 3-Hydroxy-4-[2-(2-methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyrylamino]-azepane-1-carboxylic acid tert-butyl ester; 4-(4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-3-oxo-azepane-1-carboxylic acid tert-butyl ester; 4-(2-Cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyrylamino)-3-oxo-azepane-1-carboxylic acid tert-butyl ester; 4-[2-(2-Methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyrylamino]-3-oxo-azepane-1-carboxylic acid tert-butyl ester; *N*-(1-Benzenesulfonyl-3-oxo-azepan-4-yl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide; *N*-(1-Benzenesulfonyl-3-oxo-azepan-4-yl)-2-(2-methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide; 3-(4-

Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-4-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester; 4-(4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-3-oxo-azepane-1-carboxylic acid benzyl ester; and acetic acid (2S,3S)-3-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butanoylamino)-4-oxo-azetidin-2-yl ester;

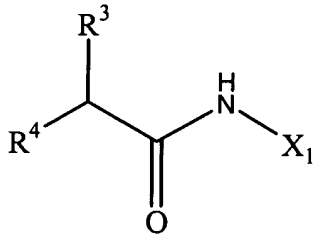
and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

28. (original) A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

29. (original) A method for treating a disease in an animal in which inhibition of Cathepsin S can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Claim 1 or a *N*-oxide derivative or individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt or solvate of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

30. (canceled)

31. (original) A process for preparing a compound of Formula I:



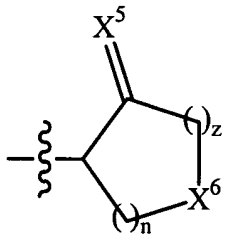
I

in which:

X^1 is $-C(R^1)(R^2)X^2$ or $-X^3$;

X^2 is cyano, -CHO, $-C(R^7)(R^8)R^5$, $-C(R^7)(R^8)CF_3$, $-C(R^7)(R^8)CF_2CF_2R^9$ $-CH=CHS(O)_2R^5$, $-C(R^7)(R^8)CF_2C(O)NR^5R^6$, $-C(R^7)(R^8)C(R^7)(R^8)NR^5R^6$, $-C(R^7)(R^8)C(R^7)(R^8)OR^5$, $-C(R^7)(R^8)CH_2OR^5$, $-C(R^7)(R^8)CH_2N(R^6)SO_2R^5$, $-C(R^7)(R^8)C(R^7)(R^8)N(R^6)(CH_2)_2OR^6$, $-C(R^7)(R^8)C(R^7)(R^8)N(R^6)(CH_2)_2NR^6$ or $-C(R^7)(R^8)C(R^7)(R^8)R^5$; wherein R^5 is (C_{1-4})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{4-10})aryl(C_{0-6})alkyl, (C_{4-10})cycloalkyl(C_{0-6})alkyl or hetero(C_{4-10})cycloalkyl(C_{0-6})alkyl; R^6 is hydrogen or (C_{1-6})alkyl; R^7 is hydrogen or (C_{1-4})alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo; R^9 is hydrogen, halo, (C_{1-4})alkyl, (C_{5-10})aryl(C_{0-6})alkyl or hetero(C_{5-10})aryl(C_{0-6})alkyl;

X^3 represents a group of Formula (a):



(a)

in which n is 1 or 2, z is 0 or 1, X^5 is selected from NR^{10}, S or O, wherein R^{10} is hydrogen or (C_{1-6})alkyl, and X^6 is O, S or NR^{11}, wherein R^{11} is selected from hydrogen, (C_{1-6})alkyl, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4S(O)_2R^{14}$, $-R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4C(O)NR^{12}R^{15}$ and $-X^4S(O)_2NR^{12}R^{15}$, in which X^4 is a bond or (C_{1-6})alkylene; R^{12} at each occurrence independently is hydrogen or (C_{1-6})alkyl; R^{13} is hydrogen, (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl, R^{14} is (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl and R^{15} is (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-12})bicycloaryl(C_{0-6})alkyl;

wherein within X^1 any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical R^{20} selected from $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{15}R^{12}$,

$-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$; and wherein X^1 and R^{20} may be substituted further with 1 to 5 radicals independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$ wherein X^4, R^{12}, R^{13}, R^{14} and R^{15} are as defined above;

R^1 and R^2 are both fluoro; or

R^1 is hydrogen or (C_{1-6})alkyl and R^2 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, cyano, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{15}R^{12}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, wherein X^4, R^{12}, R^{13}, R^{14} and R^{15} are as defined above; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8})cycloalkylene or hetero(C_{3-8})cycloalkylene; wherein R^2, said cycloalkylene and said heterocycloalkylene may be substituted further with 1 to 3 radicals independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$, wherein X^4, R^{12}, R^{13} and R^{14} are as defined above;

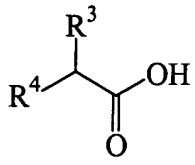
R^3 and R^4 are independently $-C(R^{16})(R^{17})X^7$, wherein R^{16} and R^{17} are hydrogen, (C_{1-6})alkyl or fluoro, or R^{16} is hydrogen and R^{17} is hydroxy and X^7 is selected from $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$,

$-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{15}R^{12}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, wherein X^4, R^{12}, R^{13}, R^{14} and R^{15} are as defined above;

wherein within one of R^3 or R^4 any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical R^{21} selected from $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{12}R^{15}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, wherein X^4, R^{12} and R^{15} are as defined above; and wherein each of R^3, R^4 and R^{21} may be substituted further with 1 to 5 radicals independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$, wherein X^4, R^{12}, R^{13} and R^{14} are as defined above; provided that only one bicyclic ring structure is present within each of R^3 or R^4; and provided that when X^2 is cyano and X^7 within one of R^3 or R^4 is $-X^4C(O)R^{13}$ or $-X^4C(O)R^{15}$, wherein X^4 is a bond, then X^7 within the other of R^3 or R^4 is limited to $-X^4SR^{15}$, $-X^4S(O)R^{15}$ and $-X^4S(O)_2R^{15}$, wherein R^{15} is (C_{6-10})aryl(C_{1-6})alkyl substituted with 1 to 5 radicals or hetero(C_{5-10})aryl(C_{0-6})alkyl optionally substituted with 1 to 5 radicals, wherein said radicals are independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$, wherein X^4, R^{12}, R^{13} and R^{14} are as defined above, provided that the radical is not selected from only halo when R^{15} is (C_{6-10})aryl(C_{1-6})alkyl; and provided that when X^2 is cyano then X^7 within R^3 and R^4 is not $-X^4C(O)NR^{12}R^{12}$, $-X^4C(O)NR^{15}R^{12}$ or $-X^4C(O)NR^{18}R^{19}$, wherein X^4 is a bond and R^{18} and R^{19} together with the nitrogen atom to which they are attached form hetero(C_{3-10})cycloalkyl or hetero(C_{5-10})aryl;

and the corresponding N-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds of formula I and their N-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; which process comprises:

(A) reacting a compound of Formula 2:



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with a compound of the formula $NH_2CR^1R^2X^2$, in which X^2, R^1, R^2, R^3 and R^4 are as defined in the Summary of the Invention for Formula I; or

(B) reacting a compound of Formula 2 with a compound of the formula NH_2X^3, in which X^3, R^3 and R^4 are as defined in the Summary of the Invention for Formula I; or

(C) optionally converting a compound of Formula I into a pharmaceutically acceptable salt;

(D) optionally converting a salt form of a compound of Formula I to non-salt form;

(E) optionally converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;

(F) optionally converting an *N*-oxide form of a compound of Formula I its unoxidized form;

(G) optionally resolving an individual isomer of a compound of Formula I from a mixture of isomers;

(H) optionally converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and

(I) optionally converting a prodrug derivative of a compound of Formula I to its non-derivatized form.

REMARKS

Claims 1-29 and 31 are pending in this application.

The Applicants seek to clarify a statement made by the Examiner regarding the double patenting rejection. In the June 11, 2003 Office Action the Examiner stated: "The difference between Graupe et al. '128 and the instant claim is that variable X^5 of formula I of Graupe et al. can be hydrogen or alkyl, while it is hydrogen in the instant compound." The Applicants' believe the Examiner intended, instead, to state: "The difference between Graupe et al. '128 and the instant claim is that variable X^5 of formula I of Graupe et al. can be hydrogen, while it is hydrogen or alkyl in the instant compound." In the structure from the Graupe, et. al. '128 application, as correctly described by the Examiner on the bottom of page seven of the Office Action dated June 11, 2003, X^5 of formula I can only be hydrogen and not selected from hydrogen or alkyl. For the instant Application, the comparable group of the compound of formula I(b), as correctly described by the Examiner on the top of page seven of the same Office Action, may be hydrogen or alkyl. The Applicants request that the Examiner clarify if this was his intention.

RESTRICTION REQUIREMENT

The Applicants submit that the restriction requirement in this Application is improper. The particular issue here is whether the U.S.P.T.O. has the authority to compel an applicant to divide up her or his generically claimed invention pursuant to an election of species requirement. The Applicants submit that the P.T.O. does not have this authority. If, in order to comply with the Restriction Requirement, the Applicants are compelled to divide their generically claimed invention into various subgenus claims, the Applicants will not have their claims examined in the form that they believe best to define their invention. Decisions by the Patent and Trademark Office Board of Patent Appeals and its reviewing court clearly hold that a restriction requirement which compels an applicant to divide a generic claim for the purposes of excising non-elected subject matter is improper and that such a procedure amounts to a rejection.

The Examiner cites two cases, *In re Harnisch* and *Ex parte Hozumi*, to support the position that the Restriction Requirement is proper. The Applicants bring to the attention of the Examiner that these decisions are not about restriction practice. *In re Harnish* and *Ex parte Hozumi* deal with improper Markush group rejections. While the Examiner has used terminology in Section 3 of the Office Action typically associated with improper Markush group rejections, i.e. the compounds within the group "do not share a common utility" or "do not share a substantial structural feature disclosed as being essential to that utility," the Examiner does not set forth any arguments to support an improper Markush group rejection. Setting forth a conclusion that the elements of an improper Markush grouping exist, without explaining why it is believed these elements are present, does not constitute a prima facia case for an improper Markush group rejection. Accordingly, the Applicants do not believe the Examiner is making an improper Markush group rejection.

The Applicants believe that the Examiner has intertwined elements of restriction practice with those required to support an improper Markush group rejection. Restriction practice is distinct from a rejection of a claim due to a lack of unity of invention. The Examiner cites M.P.E.P. §§ 806.04 and 803.02 in support of the contention that the restriction requirement of a generic claim is allowed when species within it are independent. However, the proper treatment of the restriction of Markush-type claims is described in § 803.02 of the M.P.E.P. This section states in relevant part:

> In applications containing claims of that nature [Markush-type], the examiner may require a provisional election of a single species prior to examination on the merits. The provisional election will be given effect in the event that the Markush-type claim should be found not allowable. Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable over the prior art, examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration.

If the elected claims encompass more than one species, the Examiner may require that the Applicants elect a particular species for examination; however, this is a procedural tool and there is nothing found in the statutes, regulations, procedures, or case law which provides that the Applicants must amend the scope of a generic claim to excise non-elected species. This is reiterated in § 809.02(c) of the M.P.E.P.:

> An examiner's action subsequent to an election of species should include a complete action on the merits of all claims readable on the elected species.
>
> ....
>
> (B) When a generic claim is subsequently found to be allowable, and not more than a reasonable number of additional species are claimed [in different claims], treatment shall be as follows:
>
> (1) When all claims to each of the additional species are embraced by an allowable generic claim as provided by 37 CFR 1.141, applicant must be advised of the allowable generic claim and that claims drawn to the non-elected species are no longer withdrawn since they are fully embraced by the allowed generic claim.

(Emphasis added.) The Applicants point out the "a reasonable number" of species refers to those *specifically* enumerated by a claim and not to the number of species embraced by the generic claim.

The examiner may require an applicant to elect provisionally a species for examination. If the elected species is ultimately found patentable, then examination is extended to the provisionally withdrawn subgenera. If a species is examined on the merits and found unpatentable, the Examiner then may reject any claims which read on the unpatentable species. This rejection may be overcome by amendment. Thus, the prior art search is not extended unnecessarily and the applicant's invention, as he or she contemplates it, is examined on the merits.

Hence, while it is proper to restrict a generic claim in the manner described above, it is improper to permanently withdraw from consideration all of the non-elected species. If, after an election and an examination on the merits, the examiner believes that the generic Markush claim contains subject matter that lacks unity of invention then the examiner may make a rejection based on an improper Markush grouping accompanied by sufficient evidence by way of remarks to support the rejection.

The Examiner further argues in very general terms that the claims contain distinct and independent inventions and are thus subject to restriction. The Examiner cites *In re Papesch* and *In re Lalu* to support this contention. The Applicants respectfully submit that the issue is not whether the Applicant's generic claims encompass independent and distinct inventions. The Applicants do not make any assertions one way or the other in this regard. The Applicants contend that under standard restriction practice Markush claims are treated differently than independently claimed inventions. The Applicants direct the attention of the Examiner to § 803.02 of the M.P.E.P. which states:

> A Markush-type claim can include independent and distinct inventions. This is true where two or more of the members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. 103 with respect to the other member(s).

The Examiner states in the June 11, 2003 Office Action that "[e]ach group of the restriction requirement is directed to or involves compounds and their processes of making which are recognized in the art as being distinct from one another because of their diverse chemical structure, their different chemical properties, modes of action, different effects and reactive conditions." The Examiner goes on to argue that "a reference anticipating compounds of any one group [within the Applicants' generic Claim 1] would not render another group [within the Applicants' generic Claim 1] obvious." While making no assertions about the diversity of Markush group members in the claims of this Application, the Applicants submit that § 803.02 specifically allows a Markush claim to contain members that are diverse enough that prior art making one member obvious would not make another obvious.

In re Harnisch itself discusses how groups included in a Markush group may be diverse. Citing *Ex parte Clark*, 11 USPQ 52 (Com. Pat. 1931), the *Harnsich* court "... noted that 'the inclusion in Markush groups of compounds which differed widely in some respects,' namely, aliphatic, aromatic, and aralkyl compounds, had been permitted." *Harnisch* at 722. The Harnisch court also cited other similar cases: "It [Ex parte Clark] cited Ex parte Dahlen, 42 USPQ 208 (Bd. App. 1938) as permitting the grouping of compounds having the same nuclei but side chains wherein there was a wide variation." *Harnisch* at 722. Accordingly, even if the Applicants' claimed invention can be construed to contain independent and distinct subject matter, a Markush grouping containing diverse groups is acceptable practice.

The Restriction Requirement will require the withdrawal of entire claims that are sub-genuses of the most generic Markush claim, as well as parts of individual claims. The M.P.E.P. does not allow either practice. Entire claims that are dependent on the most generic claim of the invention are allowed to contain independent and distinct inventions. The Applicants direct the Commissioner to 37 C.F.R. § 1.141 (a) (2003):

> Two or more independent and distinct inventions may not be claimed in one national application, except that more than one species of an invention, not to exceed a reasonable number, may be specifically claimed <u>in different claims</u> in one national application, provided that the application also includes an allowable claim generic to all the claimed

> species and all the claims to species in excess of one are written in dependent form (§ 1.75) or otherwise include all the limitations of the generic claim. (Emphasis added.)

In Claims 8, 9, 13-15, and 25-27, the Applicants' have claimed species of the generic Claim 1. Even assuming these species claims represent independent and distinct inventions, they include all of the limitations of the generic claim from which they depend. Written in such a manner, it is entirely proper for the Application to contain species claims that may be independent and distinct.

In addition to requiring the permanent withdrawal of Claims 8, 9, 13-15, and 25-27 in their entireties, the Examiner also has required that the Applicants excise subject matter *permanently* from within the most generic Claim 1, as well as from within individual Claims 2-7, 11-12, and 16-24 (species of Claim 1), Claim 28 (the pharmaceutical composition of a compound from Claim 1), Claim 29 (the method of treating with a Claim 1 compound), and Claim 31 (a process for preparing a Claim 1 compound). All of which depend from generic Claim 1. This practice has been prohibited by the courts. The Applicants again direct the Examiner's attention to *In re Haas,* 486 F.2d 1053 (C.C.P.A. 1973) (*Haas I*) (further proceedings at *In re Haas*, 580 F.2d 461 (C.C.P.A. 1978)). In that case, the examiner, relying on 35 U.S.C. § 121,[1] objected to two Markush claims as each being drawn to multiple patentably distinct inventions and withdrew them both from further consideration. A species claim was allowed and a "narrow Markush claim, encompassing only those reactive moieties similar to the allowed species, was suggested" (*Haas I* at 1054). The applicants were then compelled to cancel the original claims.

The prosecution history for this Application follows the facts in *Haas I* very closely. Here, the Examiner required the Applicants to elect a single disclosed species from Markush claims and all non-elected species were required to be withdrawn permanently from further consideration. The Applicants elected a single species for examination purposes with traverse but did not cancel the non-elected species from the claims. In an Office Action dated June 11, 2003, Claims 8, 9, 13-15, and 25-27 were withdrawn permanently from further consideration by the Examiner as claiming non-elected subject matter. Claims 1-7, 11, 12, 16-24, 28, 29, and 31 were objected to as containing non-elected subject matter within each claim which the Examiner requires to be removed. The *Haas I* court held that an objection of this sort can deny the applicant's substantive rights and amount to a rejection of those

[1] Section 121 states: "If two or more independent and distinct inventions are claimed in one application, the Director may require the application to be restricted to one of the inventions".

claims. In *Haas I*, as well as in this Application, the requirement to cancel claims containing non-elected species was made permanent. This amounted to a rejection as each claim, in its entirety, would never be examined on the merits, essentially denying the patentability of the Applicants' invention as they see fit to claim it. In this regard, the court in Hass I held,

> [t]he absolute "withdrawal" herein cannot properly be categorized as merely a "requirement" or "objection" and the avenue of review thereby be restricted to petition and judicial examination under 5 USC § 701-6. An examiner's adverse action of this nature is a rejection, a denial of substantive rights. Review thereof must fall within the jurisdiction of the board.

Id. at 1056. The Examiner's requirement to cancel the non-elected species from the generic claim thus amounts to a rejection of the claims and is a denial of substantive rights which is improper and appealable to the Board and its reviewing court.

The Court in *In re Weber*, 580 F.2d 455 (C.C.P.A. 1978) addressed this same situation. The examiner asserted that Weber's claim 1 "embraced 24 enumerated independent and distinct inventions" (*id.* at 456) and subsequently rejected it for misjoinder under 35 U.S.C. § 121. Upon appeal the Board affirmed that "§ 121 was an adequate legal basis for the examiner to reject a single claim 'embracing' more than one independent and distinct invention." (*Id.* at 457). However, upon appeal to the United States Court of Customs and Patent Appeals, the court held that the restriction requirement was improper, stating:

> As a general proposition, an applicant has a right to have each claim examined on the merits. If an applicant submits a number of claims, it may well be that pursuant to a proper restriction requirement, those claims will be dispersed to a number of applications. Such action would not affect the right of the applicant eventually to have each of the claims examined in the form he considers to best define his invention. If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on the merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the subgenera would be defined by the examiner rather than by the applicant, it is not inconceivable that a number of the fragments would not be described in the specification.

Id. at 458 (emphasis added). The *Weber* court is particularly clear that the division of a single claim by the examiner, with the non-elected subject matter being withdrawn from further consideration, is not permissible. In this Application, the Examiner has required that the Applicants divide their generic claims into multiple parts denying them an examination of their invention as a whole.

Please see also *Ex parte Holt*, 214 USPQ 381 (Bd. App. 1982) (*Holt I*) (subsequent proceedings at *Ex parte Holt*, 218 U.S.P.Q. 747 (B.P.A.I. 1982) and *Rohm and Haas Company v. Robert Gottschalk, Commissioner of Patents,* 504 F.2d 259 (D.C. Cir.1974) for similar holdings.

In light of *Weber* and *Haas*, the Patent and Trademark Office revised restriction practice with respect to generically claimed inventions. The proper procedure for restricting a generic claim is delineated in M.P.E.P. § 803.02 (2001). In this regard the Appellants direct the Commissioner to M.P.E.P. § 803.02, paragraphs 4 and 5, which states:

> As an example, in the case of an application with a Markush-type claim drawn to the compound C-R, wherein R is a radical selected from the group consisting of A, B, C, D and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD or CE. The Markush-type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the non-elected species would be held withdrawn from further consideration. As in the prevailing practice, a second action on the rejected claims would be made final.
>
> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended.

(Emphasis added.) This section of the M.P.E.P. makes clear that if the elected species is ultimately found patentable, then the examination is to be extended to the provisionally withdrawn matter. If, on the other hand, the elected species is found unpatentable, the generic claim and claims to the elected species are rejected and claims to the non-elected subgenera are withdrawn from further consideration. The applicant may overcome this rejection by amending the generic claim to exclude the unpatentable species. If after reconsideration of the amended claim a second species is found unpatentable, the claim is rejected and the action is made final.

The Examiner referred the Applicants to M.P.E.P. § 806.04(f) (2001), "Claims Restricted to Species, by Mutually Exclusive Characteristics," as the basis for the withdrawal of the non-elected subject matter. Section 806.04(f) states, in part, that "[t]he general test as to when claims are restricted, respectively, to different species is the fact that one claim recites limitations which under the disclosure are found in a first species but not in a second, which a second claim recites limitations disclosed only for the second species and not the first," (emphasis added). Please note the plurality of

"claims" in the above excerpt and the fact that the section is referring to restriction between more than one species claims and not within one genus claim. The Applicants submit that § 806.04(f) does not support the proposition that the Patent Office has the authority under 35 U.S.C. § 121 (2003) to permanently withdraw non-elected species and compel an amendment narrowing the scope of an applicant's generically claimed invention. See also *In re Watkinson*, 900 F.2d 230, 232 (Fed.Cir.1990) and *Weber* at 460 for support of this contention.

In this Application, the Examiner goes further by drafting a claim for the Applicants. Hence, the Examiner, rather than the Applicants, defines the form in which the invention is claimed. The Applicants respectfully submit that such an action is improper. An applicant has a right to have each claim examined on the merits in the form she or he considers to best define her or his invention. (See 35 U.S.C. § 112, second paragraph.) It is not in the Examiner's purview to define the Applicant's invention for them. The Applicants refer the Commissioner to *In re Wolfrum*, 486 F.2d 588, 591 (C.C.P.A. 1973) where the court stated "[u]nder this provision of § 112, the scope of the subject matter is governed not by the examiner's conception of the 'invention' but by that 'which the applicant regards as his invention.'" Also *Weber* at 458 speaks to this issue: "[a]n applicant is given, by the statute, the right to claim his invention with the limitations he regards as necessary to circumscribe that invention." Here the Examiner has drafted a genus claim and in doing so defines the invention for the Applicants. The Applicants respectfully submit that this action is clearly improper.

Finally, the Examiner stated in the November 6, 2002 Office Action, "[d]ifferent search considerations are involved with each of the group[*sic*] listed above and would impose an undue burden on the Examiner and the Patent office's resources if unrestricted." The Applicants respectfully submit that when there is a conflict between an applicant's statutory right to claim the subject matter of her or his invention as she or he sees fit and the Patent Office's power to regulate the workload of its Examiners, the rights of the applicant must prevail. The Applicants are mindful of the Patent Office's interest in limiting the burden of the examination in each application. The Court in *Weber* recognizing this interest stated, "[e]ven though the statute allows the applicant to claim his invention as he sees fit, it is recognized that the PTO must have some means for controlling such administrative matters as examiner caseloads and the amount of searching done per filing fee." *Weber* at 458. However, the court went on to state that "... in drawing priorities between the Commissioner as administrator and the applicant as beneficiary of his statutory rights, we conclude that the statutory

rights are paramount." *Id.* at 458-459. The Applicants submit that their right to claim generically their invention prevails over the Patent Office's power to restrict.

The Examiner finds all of these arguments unpersuasive. The Applicants have searched without success for some sort of statutory or judicial authority supporting the Examiner's objection. To the contrary, the authority decisively demonstrates that the present objection to the Claims is improper. Accordingly, the Applicants submit that there is no basis for the objection to Claims 1-29 and 31 and respectfully request that the Restriction Requirement be withdrawn.

REJECTION UNDER 35 USC § 101

The Examiner rejected Claim 30 under 35 USC § 101. Claim 30 was deleted. Accordingly, the Applicants request that this rejection be withdrawn.

OBJECTION

The Examiner objected to Claims 11-12 as being dependent upon a rejected base claim and containing non-elected subject matter. The Examiner objected to Claims 1-7, 16-24, 28-29 and 31 as containing non-elected subject matter. The Examiner indicated that the claims would be allowable if the non-elected subject matter were deleted. In view of the Applicants' remarks above with regard to the Restriction Requirement, the Applicants submit that this objection to the claims is overcome and respectfully request that it be withdrawn.

TERMINAL DISCLAIMER

The Examiner provisionally rejected Claim 10 under the judicially created doctrine of obvious-type double patenting over Claim 1 of copending application No. 10183128. The Applicants direct the Examiner's attention to M.P.E.P. § 804 (I) (B), "[i]f the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent...". Applicants believe that all claims now pending in this Application are in condition for allowance and the provisional, nonstatutory double patenting rejection is the only rejection remaining in the Application. Pursuant to the M.P.E.P. § 804